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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/177,843	10/22/1998	JOHN LOIKE	48940-A-PCT-	3650

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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	24

DATE MAILED: 04/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/177,843	LOIKE ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *1-26 and 42-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-39 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/4/03 has been entered.

2. Claims 1-54 are pending in the instant application. Claims 1-26, 42-54 are withdrawn from further consideration as being drawn to a non-elected invention. Applicant is reminded to cancel all claims drawn to a non-elected invention.

3. Therefore, claims 27-39, and 41 are examined on the record.

Claims Rejections Withdrawn - 35 USC § 112, 1st paragraph

4. The rejection of claims 27-39 under 35 USC 112, 1st paragraph as lacking an enabling disclosure is withdrawn in view of the amendment and arguments set forth by the applicant.

Claim Rejections - 35 USC § 112,2nd paragraph

5. Claims 27-39, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. With regard to claim 27 and dependent claims thereof in the recitation of the term "effective amount", it is unclear from the specification as to the amount intended. Any amount added if in enough quantity would become inhibitory.

7. With regard to claim 27 and dependent claims thereof in the recitation of the term "antibody", it is unclear as to which b1 antibody is being referred. There are multiple b1 integrin antibodies available that would fall within the scope of the claims, it is not clear if all are intended.

Claim Rejections - 35 USC § 112, 1st paragraph

8. Claims 27-39, and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a malignant tumor which comprises the administration of the P4C10 beta 1 integrin antibody, a beta 1 integrin receptor antibody fragment, or a peptide consisting of GRGDSP does not reasonably provide enablement for a method of treating a malignant tumor which comprises the administration of any and all antibodies to beta 1 integrin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant invention is drawn to a method of treating a malignant tumor in a subject wherein the tumor is surrounded by the extracellular matrix protein tenascin, comprising the administration an agent wherein the agent is an antibody to beta 1 integrin, a beta 1 integrin antibody fragment, or a peptide comprising the sequence GRGDSP. The premise of the instant invention is that beta 1 integrins found on the surface of leukocytes prevented the infiltration of the tumor because said integrins bind

to the tenascin which surrounds the tumor. Therefore, if an antibody or antibody fragment directed against the beta 1 integrin is added, it would interfere with integrin-tenascin binding and thereby allow the infiltration of leukocytes into the tumor.

The instant specification has taught one of skill in the art a method of administering a peptide comprising SEQ ID No: 2, an antibody termed P4C10, and a Fab2 antibody fragment. The scope of the claims however read on any and all beta 1 integrin antibodies of which the instant specification has not taught. It is well established fact that the discovery of antibodies for in vivo usage is often difficult to accomplish. Seaver SS (Genetic Engineering News 1994 Aug;10:10 & 22) states that the discovery of specific antibodies for therapeutic usage is difficult and tedious. Seaver SS further states that the other "biological factors" such as specificity, bioavailabilty, and the ability of the antibody to reach its target are problems and situations that must be test before an antibody is able to function as a therapeutic (see page 21 columns 2-5). Others have disclosed that other factors, including cross-reactivity, low tumor uptake, and immunogenicity play a critical role in the use of antibodies in vivo. Reilly *et al* (Clin Pharmacokinet 1995;28(2):126-142) disclose that incomplete screening of normal tissue for antigen believed to be tumor specific can lead to detrimental effects of normal tissue (see page 129). Reilly *et al* further disclose that the administration of foreign antibodies to a host can elicit immunogeneic responses resulting in rapid elimination of the antibody thereby rendering the therapy ineffective. Therefore, given the fact that the instant specification has only taught one specific beta1 antibody, one of skill in the art would be forced into large amounts of experimentation because several factor regarding

antibodies to beta 1 integrin have not been taught. The specification has not taught what if any effects the binding of the antibody to other cells expressing beta 1 integrin may have on the host, method of screening for other antibodies and how to determine if the antibodies are available at the site of interest. Furthermore, the specification has not taught how to avoid premature elimination of the antibody from the host or if immunogeneic responses are elcited from any other antibody.

Therefore, given the fact that the art teaches unpredicatability as it applies to the antibody arts, and the lack of information disclosed by the instant specification as it applies to other antibodies (i.e. screening methods and testing), one of skill in the art would be forced into undue experimentation to practice the instant invention commensurate in scope to the claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 27,28,29 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Bourdon *et al* (WO 92/07872). Claims are drawn to a method of administering to a subject an agent that binds to leukocyte cells, wherein the agent is a peptide comprising the peptide of GRGDSP (SEQ ID No: 2), further limited by a subject of which is a human. Bourdon *et al* disclose of a method of inhibiting the attachment of cells to

tenascin comprising the administration of a peptide comprising the sequence of SEQ ID No: 2 and further contemplate the use of the method in a human (see page 32).

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

12. Claims 27, 28-29, and 41 are rejected under 35 U.S.C. 102(e) as being anticipated by Ruoslahti *et al* (5,981,478). Claims are drawn to a method comprising the administration of an agent wherein the agent is a peptide of SEQ ID No: 2 and wherein the administration is to a human. Ruoslahti *et al* disclose a method comprising the administration of a peptide sequence that comprises that of SEQ ID No: 2 and wherein the administration is in a human. Furthermore, Rouslahti *et al* disclose that integrins are involved in cancer cell metastasis, and that ligands that are able to bind to the ligand may be applicable for the modulation of integrin activities.

Conclusion

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
April 6, 2003

ALI R. SALIMI
PRIMARY EXAMINER